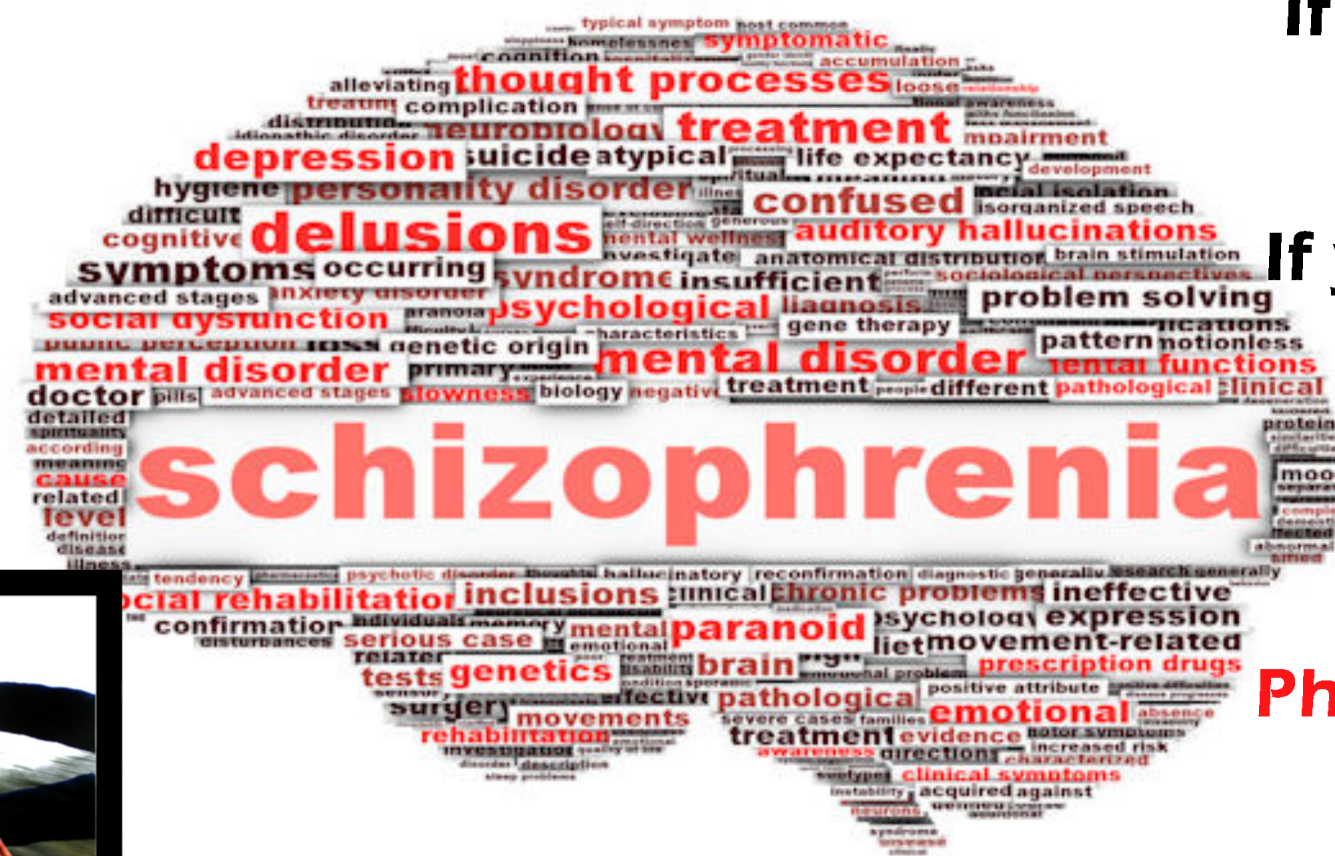
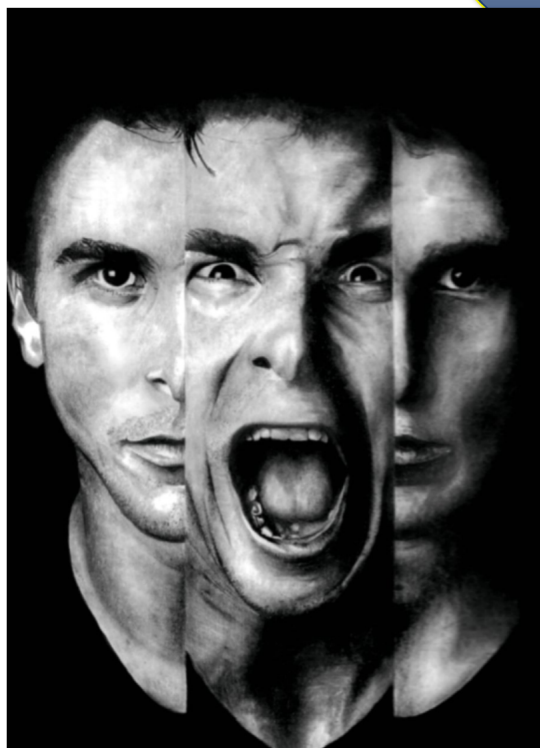


Draw Pharmacology in your mind



**If you are a pharmacy student
If you are postgraduate and want
to revise pharmacology by an
easy way**

If you are using any pharmacology reference

this file will aid you

> And wait for more <

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لا تتسوني من صالح دعائكم

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Psychosis (Schizophrenia)

- Chronic debilitating psychotic mental disorder
- Affects 1% of people
- Begins at late adolescence and usually continues throughout life**
- May have a hereditary origin

Symptoms

+ve symptoms

1. Auditory hallucinations
2. Delusions
3. Illusions
4. Hyper responses

-ve symptoms

1. Inability to pay attention (cognitive impairment)
2. Disorganization of thoughts and speech
3. Loss of sense of pleasure (anhedonia)
4. Loss of will and drive
5. Social withdrawal
6. Deficiency of short-term verbal and non-verbal memory
7. Mask-like face

Etiology

It is thought that it is caused by **early and irreversible brain abnormalities** occurring in the first few months of prenatal life as a result of:

1. Maternal viral infection
2. High blood pressure

Causes

Abnormal **dopamine** transmission in:

1. Mesolimbic pathway
2. Mesocortical pathway

This is called "**Dopamine hypothesis**"

Evidence of Dopamine hypothesis

1. **Amphetamine and Cocaine**
↑ DA transmission → induce psychosis
2. **Antipsychotic drugs**
Acts mainly by ↓ DA transmission by blocking D₂ receptors → relieve symptoms
3. **Post-mortem imaging studies** in brain of schizophrenic patients demonstrate raised DA amount (due to down-regulation of Dopaminergic receptors in some regions)

Drawbacks of Dopamine hypothesis

1. Antipsychotics relieve **some** symptoms
 2. DA metabolites still in normal range
- So, schizophrenia's causes **not just ↑ DA**, other neurotransmitters are involved just like **5HT and Glutamate**
 - So, **treatment goal Blocking DA &/or 5HT receptors in the "limbic system"**

Antipsychotics

Mechanism

They block **D₂ receptors** mainly as well as some other receptors

Examples

Phenothiazines:

- Chlorpromazine
- Promethazine
- Fluphenazine
- Thioridazine

Buterophenones:

- Haloperidol

Thioxanthenes:

- Thiothixene



Typical

Mechanism

They block **5HT₂ receptors** mainly as well as **D₂ receptors**

Atypical

Examples

- Clozapine
- Risperidone
- Quetiapine
- Aripiperazole



Actions

- Antipsychotics mainly **block D₂ &/or 5HT receptors** in the limbic system reducing the positive symptoms of schizophrenia

- Typical antipsychotics** have the ability to block:

1. Dopaminergic receptors
2. Cholinergic receptors
3. α-adrenergic receptors
4. Histaminergic receptors

These receptors may exist outside the limbic system (in the nigrostriatal pathway - extrapyramidal system and tuberoinfundibular system) so, **Typical antipsychotics have many side effects**

80% of the therapeutic effectiveness of antipsychotics is due to their ability to **block D₂ receptors in the limbic system**

Uses

Mania

Newer antipsychotics are often used with Li salts in initial treatment of mania ex. **Aripiperazole**



Nausea & Vomiting

Prevention of severe N & V associated with radiation or cancer chemotherapy → **due to their action on CTZ**

Schizophrenia

- Typical antipsychotics** → alleviate **+ve** symptoms + **No effect on -ve symptoms**
- Atypical antipsychotics** → alleviate **-ve** symptoms > **+ve symptoms**

Atypical antipsychotics can be used in patients **resistant** to typical antipsychotics - decrease negative symptoms



Clozapine

- Has low affinity to dopaminergic receptors and high affinity to 5HT₂ receptors → less side effect
- However it has some extrapyramidal and antimuscarinic side effects
- Has D₄ receptors blocking activity → so it is thought that D₄ receptors are responsible for -ve symptoms

Aripiprazole

- Is the most commonly used antipsychotic now as it has **no extrapyramidal effects and no antimuscarinic effects at all**

Both typical and atypical antipsychotics have α-adrenergic blocking effect and causing postural hypotension

Some notes

Antipsychotics

Side effects

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Sedation - Confusion

6. Antihistaminic action

Postural hypotension

5. α-adrenergic blockade

4. Antimuscarinic effects

3. Hyperprolactinemia

1. Parkinsonism

Notice that

If the antipsychotic drug has some **anticholinergic activity** → this will inhibit cholinergic activity of Ach in the nigrostriatal pathway → leading to milder extrapyramidal side effects

So, Anticholinergic effects could be beneficial

Examples:

1. Thioridazine

Has strong anticholinergic activity → mild extrapyramidal side effects

2. Haloperidol , Fluphenazine

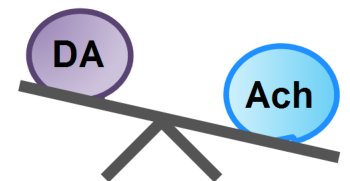
Weak anticholinergic activity → severe extrapyramidal side effects

Extrapyramidal side effects

Antipsychotics block DA receptors in nigrostriatal pathway (extrapyramidal system) → so, there will be a relative predominance of cholinergic activity (*cholinergic activity will increase*) → Parkinson's like symptoms

Symptoms:

1. Difficulty in swallowing
2. Protrusion of the tongue
3. Tremors at rest
4. Shuffling gait
5. Akathisia (inability to sit still) (irritability)



1. Dry mouth
2. Blurred vision
3. Constipation
4. Urine retention
5. Glaucoma

But as we said in this case **antimuscarinic effects are beneficial to overcome extrapyramidal symptoms**

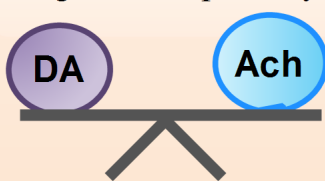
↓ dopamine in tuberoinfundibular system →
↑ prolactin hormone → hyperprolactinemia
so, **infertility and gynecomastia in males**

2. Tardive dyskinesia

- Involuntary movements of tongue, jaw, face and limbs and also **delayed voluntary movements**
- This is due to long-term treatment by typical type

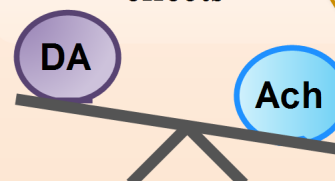
Etiology

At first **normal balance** between Ach and DA at nigrostriatal pathway



After **short-term treatment** by typical antipsychotic → it will block D₂ receptors in the nigrostriatal pathway → extrapyramidal side effects (parkinsonism)

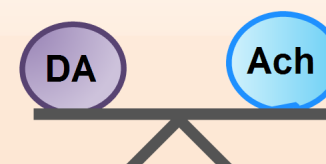
Extrapyramidal side effects



By adaptive mechanisms to overcome the blocking of D₂:

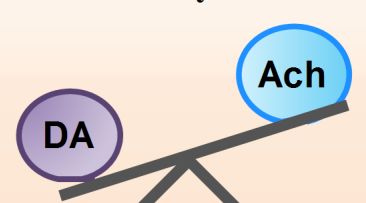
1. Receptor up-regulation occur → **NEW D₂** receptors are synthesized
 2. **Sensitivity** of the receptors to DA **increase**
- So, the dopaminergic action will be restored to normal

Transient disappearance of the extrapyramidal side effects !



If treatment continues (**long-term treatment - several years**), **MORE dopaminergic receptors will be synthesized** so, the dopaminergic activity passes beyond normal → **tardive dyskinesia**

Tardive dyskinesia



How to avoid ?

- Use the minimal effective dose from the start of treatment
- Gradually decrease the dose if tardive dyskinesia started to appear
- **Take care** → sudden withdrawal would worsen the case *cause all receptors would be unblocked !*
- **Note that** → Atypical antipsychotics have **lower risk** to extrapyramidal side effects and tardive dyskinesia